REMARKS

Claims 1, 3, 10-12, 17-20, 23-27, 34-38, 42-44, 47, 49-52, 54-56, 58 and 59 are pending. The Examiner has withdrawn claims 2, 4-8, 13-16, 21, 22, 28, 29, 31, 40, 41, 45, 46, 48 from consideration as being drawn to a non-elected species and these non-elected claims are hereby canceled without prejudice with Applicant reserving the right to pursue the subject matter covered therewith in future divisional applications.

Claims 1, 17, 26 and 37 have been amended to more particularly point out and distinctly claim the subject matter which the applicant regards as her invention. Claims 1 and 26 have been amended to recite "wherein the second therapeutic agent does not include nitric oxide synthase"; support for the positive recitation of nitric oxide synthase may be found in the specification as filed *inter alia* page 18, line 5. Claim 17 has been amended to delete "biocompatible" and insert "polymeric", antecedent basis for which is found in claim 1 on which this claim depends. Claim 37 has been amended to delete "and said carrier is an early expression carrier" to now recite a "vector is a delayed expression vector", support for which may be found in the specification as filed *inter alia* page 13, lines 3-4. No new matter has been added. Applicants respectfully request entry of this amendment.

Claim of Priority to U.S. 09/204,254, now U.S. Patent No. 6,369,039

Examiner previously entered Applicant's claim to the benefit of the prior-filed copending nonprovisional application U.S. Ser. No. 09/204,254, filed December 3, 1998 now U.S. Patent No. 6,369,039 B1 ("'039").

In the October 29, 2003 Advisory Action, the Examiner acknowledges that the '039 specification lists various therapeutic agents that can be in the coating, but asserts that nothing in the '039 specification would lead one to the particular combination as set forth in the claims. The Examiner further asserts that applicants stating that the specification of '039 provides a list of therapeutic agents and that the preceding agents can be used in combination does not lead one to the particular combination as set forth in the claims.

Applicants respectfully traverse and maintain that the '039 specification not only lists various therapeutic agents, but also explicitly guides one of skill to *combine* the various therapeutic agents, as claimed.

The '039 specification at paragraph at col. 4, line 64 to col. 5, 48 teaches which therapeutic agents can be in the coating. Therapeutic agents include gene/vector systems that can be present in the

coating (col. 4, line 67 to col. 5, line 4), angiogenic agents (col. 5, lines 15-16) as well as "vascular cell growth promoters such as growth factors" (col. 5, lines 31-32). Growth factors are proteins so they are "non-genetic" and if they promote vascular growth they are "angiogenic agents." Col. 5, line 44 specifically states that the preceding therapeutic agents can be used in combination.

The polynucleotides which may be used in the practice of the invention are described in col. 5, lines 49-54 and, moreover, the fact that the polynucleotides can also encode for therapeutic polypeptides is specifically taught. The *combination* of polynucleotides encoding therapeutic polypeptides and therapeutic polypeptides or proteins which may be used is clearly described as follows:

> "In addition, the **polypeptides or proteins that can be incorporated into the polymer coating 130, or whose DNA can be incorporated**, include without limitation, **angiogenic factors** including acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CDK inhibitors; thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, including agents for treating malignancies; **and combinations thereof**." (Emphases added)

Therefore, the '039 specification provides ample support for a combination of polynucleotides and "non-genetic" angiogenic agents in the coating. As such, the '039 patent provides a specific written description for the particular combination of a first therapeutic agent which is a vector, wherein the vector contains a first polynucleotide which encodes an angiogenic agent and a second therapeutic agent comprising a non-genetic therapeutic agent, wherein said non-genetic therapeutic agent is an angiogenic agent, as recited above in the presently pending claims and these claims should be afforded the benefit of the earlier filing date. Accordingly, applicant respectfully requests that such priority be afforded the benefit of the '039 filing date.

In view of Applicants' arguments and amendments, the Examiner has withdrawn the previous grounds for rejection under 35 U.S.C. §§ 102 and 103 and asserted the rejections below. Applicant respectfully traverses as follows.

Rejection of Claims 1, 3, 10-12, 17-20, 22-27, 30, 34-38, 42-44, 47, 49-52, 54-56, 58, 59 under 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner has rejected claim 1, 3, 10-12, 17-20, 22-27, 30, 34-38, 42-44, 47, 49-52, 54-56, 58, 59 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention at the time the application was filed.

The Examiner states that the amendment of claims 1 and 26 in the response pursuant to 37 C.F.R. § 1.111 filed March 17, 2003 adds new matter into the subject application.

The Examiner contends that the original specification does not disclose a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; and a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent.

Specifically, the Examiner states that even though the specification sets forth a list of products that the vector and carrier can carry, there is "nothing in the specification that would lead one to the particular combination set forth in the amended claims." (Final Office Action mailed June 4, 2003, page 4, lines 10-11).

Applicant respectfully traverses and maintains that the specification as originally filed specifically provides a teaching of a combination of a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; and a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent. As amended, claims 1 and 26 recite a first therapeutic agent, wherein said first therapeutic agent encodes an angiogenic agent and a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent.

MPEP 2163.05 II states:

> The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 39 USPQ2d 1895 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not **"reasonably lead"** those skilled in the art to any particular species.) [emphasis added]

Applicant asserts that the clear description in the subject specification goes well beyond one

that would merely "reasonably lead" the skilled artisan to the claimed invention, as was found lacking in *Fujikawa, supra*. Applicant respectfully asserts that one of skill in the art would not only reasonably be lead to but instantly appreciate the claimed invention when reading the specification.

The Examiner's attention is respectfully directed to page 17, lines 5-10 of the specification as originally filed, which states:

> The **first therapeutic agent of this invention comprises genetic materials** whereas the **second therapeutic agent of the invention may comprise** either genetic or **non-genetic materials**. The non-genetic material comprises any molecule or compound that induces a beneficial biological or medical reaction in vitro, or in vivo.

Further page 17, line 19 - page 18, line 16 of the originally filed specification provides examples of *non-genetic therapeutic agents* of the invention, which specifically *include angiogenic agents and factors* (page 17, line 22).

Moreover, applicant has discussed above the ample specific written description provided by the '039 patent for the pending claims, from which the subject application claims priority as a continuation-in-part.

Accordingly, the specification discloses and provides written description for angiogenic agents in both the context of the first therapeutic agent, *i.e.*, a genetic therapeutic agent encoding an angiogenic agent and second therapeutic agent, *i.e.*, a non-genetic therapeutic agent.

Therefore, contrary to the Examiner's assertion that "nothing in the specification that would lead one to the particular combination set forth in the amended claims", one of skill in the art would be adequately guided by the subject specification to combine first and second therapeutic agents as claimed.

Accordingly, the specification provides adequate written description for claims 1 and 26 as amended on March 17, 2003 and said amendments do not add new matter into the subject application. Withdrawal of this rejection is respectfully requested.

Rejection of claims 17, 30, 37, 50, 52, and 56 under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 17 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The claim has been amended to recite a polymeric coating. Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claim 30 under 35 U.S.C. § 112, second paragraph, for allegedly

being indefinite. The Examiner states that there is insufficient antecedent basis for the claim limitation, "said non-plasmid vector". Applicant intended to cancel claim 30 without prejudice in the amendment filed March 17, 2003, and has done so above. Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claim 37 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The claim has been amended to remove the recitation "said carrier". Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claim 50 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner opines that the term "small molecule" is a relative term and that one of ordinary skill in the art would not reasonably be apprised of the scope of the invention. Applicant respectfully disagrees.

In the October 29, 2003 Advisory Action, the Examiner states that the specification does not provide a definition of the term used in applicant's October 3, 2002 Response and Amendment and that there is no support or guidance in the specification that would lead one of skill in the art to the term provide or the web site cited. The Examiner further asserts that "a small molecule could be any molecule that cannot be observed by the naked eye, e.g. DNA, RNA, protein, organic compound, inorganic compound".

Applicants maintain that the term "small molecule" is a term of art which one of skill understand to be defined as a molecule of <600-700 molecular weight (*See,* Synthesis and Applications of Small Molecule Libraries, Chem. Rev. 1996 96, 555-600, attached hereto). Accordingly, applicant maintains that one of skill in the art would readily understand the term as used in the subject application and would be reasonably apprised of the scope of the claims reciting this term. The use of the term is based on the well known definition of the term, as discussed below. Applicant does not disagree that the term may encompass the molecules listed by the Examiner - if those molecules have a weight as defined by one of skill in the art. Moreover, applicant has not used the term in a way which gives a meaning repugnant to the usual meaning of the term *(See, In re Hill,* 161PQ 482 (CCPA 1947). Accordingly, the skilled artisan would know precisely what is meant by the term of art "small molecule" and as such, withdrawal of this rejection is respectfully requested.

The Examiner has rejected claims 52 and 56 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner opines that the term "site-specific" is not defined and that one of ordinary skill in the art would not reasonably be apprised of the scope of the invention. Examiner indicates an erroneous understanding of site specificity as relating to selective replication or targeting within a mammal. Applicant respectfully disagrees.

Applicant respectfully direct the Examiner's attention to the specification as filed on page 13, line 22 - page 14, line1, which describes that the "first polynucleotide integrates into the genome of cells at or around the target site" and further at page 15, lines 7-9, which refer to an example embodiment of vectors which may be used in the invention, an adenoassociated viruses, "which integrate in a stable and site-specific manner, into the genome of cells which they infect" and at page 15, lines 13-14, which describes such vectors as being able to "integrate at a specific site in the host genome". Accordingly, applicant maintains that one of skill in the art would readily understand the definition of the term site-specific, as described in the subject application,
and the term would be definite to the skilled artisan, who would be reasonably apprised of the scope of the claims reciting this term. The description provided is used according to the well known definition of the term, as discussed below. Moreover, applicant has not used the term in a way which gives a meaning repugnant to the usual meaning of the that term *(See, In re Hill*, 161PQ 482 (CCPA 1947).

In the context of vectors, the term "site-specific" is a term of art that refers to the particular locus on an endogenous DNA strand, for example a chromosome, wherein an exogenous DNA, for example vector polynucleotides such as viral DNA or transposable DNA, will integrate. The skilled artisan would appreciate that when utilizing a vector to introduce exogenous DNA into a cell, it is preferable not to have that DNA integrate at a locus such that it might disrupt the normal function of genes vital to the target cell or host organisms' health. Accordingly, it is preferable to use a "site-specific" vector that integrates at genetic loci where normal gene function is not impacted.

For example, it has been reported that an interesting feature of wild-type AAV is its site-specific integration into AAVS1, a defined locus on chromosome 19. This site specific integration is mediated by inverted terminal repeats and *Rep78/68*. It has been shown that AAV vectors mutant for the *rep* gene, lack the ability to integrate site-specifically. See: Satoh et al., Site-Specific Integration of an Adeno-Associated Virus Vector Plasmid Mediated by Regulated Expression of Rep Based on Cre-loxP Recombination. *J Virol.* 2000 November; 74 (22): 10631–10638.

Accordingly, the skilled artisan would know precisely what is meant by the term of art "site-specific" in the context of a vector and would be reasonably apprised of the scope of the claims reciting this term, and as such withdrawal of this rejection is respectfully requested.

Rejection of claims 1, 10, 11, 19, 24, 26, 34, 35, 37, 44, 49, 50, 52, 54, 55, 56, 58, and 59 under 35 U.S.C. § 102(b)

The Examiner rejects claims 1, 10, 11, 19, 24, 26, 34, 35, 37, 44, 49, 50, 52, 54, 55, 56, 58, and 59 under 35 U.S.C. § 102(b), as allegedly being anticipated by Isner U.S. Patent No. 5,652,225. The Examiner alleges that Isner teaches a method for delivery of an angiogenic factor combined with other angiogenic genes or gene products to an arterial cell. Applicants respectfully traverse.

Applicants respectfully assert that among other short comings, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent.

Applicant respectfully directs the Examiner's attention to Isner, Column 7, ¶1, which states:

> "In certain situations, it may be desirable to use DNA's [sic] encoding two or more different proteins in order [sic] optimize the therapeutic outcome. For example, DNA encoding two angiogenic proteins, e.g., VEGF and bFGF, can be used, and provides an improvement over the use of bFGF alone. **Or an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells**, while simultaneously including angiogenesis, including, for example, nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin." (Emphases added)

Accordingly, Isner, describes the possible delivery of: 1) DNAs encoding two or more different angiogenic proteins; 2) an angiogenic factor and other genes, i.e. DNAs **not encoding an angiogenic factor**; or 3) an angiogenic factor and the encoded gene products of other genes, i.e. an angiogenic factor and **a non-angiogenic gene product** [a non-genetic non-angiogenic agent]. Applicant further notes that above-reproduced paragraph provides examples of **such other non-angiogenic gene products**: "nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin", none of which are an "angiogenic protein", as defined by Isner, Column 3, lines 40-42. Moreover, none of the aforementioned gene products of other genes, i.e. genes encoding non-angiogenic products, are included as examples of an "angiogenic protein" in Isner, Column 3, lines 43-50.

However, the claims at issue recite a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent **is an angiogenic agent**.

In the October 29, 2003 Advisory Action, the Examiner asserts that "nitric oxide synthase is an angiogenic agent and applicants have provided no evidence that nitric oxide is not an angiogenic agent". Without conceding the correctness of the Examiner's position as to whether nitric oxide is an

angiogenic agent *per se*, applicant has amended claims 1 and 26 to recite the following negative limitation " wherein the second therapeutic agent does not include nitric oxide synthase". MPEP 2173.05(i) states:

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. *If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims*. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). (Emphasis added)

Nitric oxide synthase is positively recited in the specification in the paragraph at page 17, line 19 - page 18, line 16, as one of numerous alternative therapeutic agents: "Non-limiting examples of products and therapeutic agents of the invention include: ...nitric oxide synthase (NOS) .... Therefore, the specification positively recites nitric oxide synthase as an alternative element, and as such nitric oxide may be explicitly excluded in the claims.

As such Isner does not teach every element of the claimed invention. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims 1, 17, 19, 20, 26, 42, 44 and 47 under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 17, 19, 20, 26, 42, 44 and 47 under 35 U.S.C. § 103(a), as allegedly being unpatentably obvious over Isner (U.S. Patent No. 5,652,225) in view of Donovan et al., (U.S. Patent No. 5,833,651, hereinafter "Donovan").

The Examiner concedes that Isner does not teach specifically making and using a medical device comprising a biocompatible structure carrying a genetic material wherein the structure is a metallic stent. The Examiner opines that this shortcoming is overcome by Donovan which allegedly teaches stents. Applicants respectfully disagree.

As discussed above, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent, wherein the second therapeutic agent does not include nitric oxide synthase, as claimed. Donovan also fails to teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent encoding an angiogenic agent in combination with a second therapeutic agent comprising a non-genetic angiogenic, as claimed. As

such, Donovan's disclosure of metallic stents cannot cure the defects of Isner to render the claimed invention upatentably obvious.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims 1, 3, 24, 25 and 27 under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 3, 24, 25 and 27 under 35 U.S.C. § 103(a), as allegedly being unpatentably obvious over Isner (U.S. Patent No. 5,652,225) in view of Branellec et al., (U.S. Patent No. 5,851,521, hereinafter "Branellec").

The Examiner concedes that Isner does not teach specifically using an andeno-associated viral (AAV) vector in a medical device or a method of treating restenosis in a site of mechanical injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty. The Examiner opines that this shortcoming is overcome by Branellec which allegedly teaches use of AAVs a carrying a nucleic acid encoding GAX protein. Applicants respectfully disagree.

Once again, as illustrated above, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent, wherein the second therapeutic agent does not include nitric oxide synthase, as claimed. Branellec also fails to teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent encoding an angiogenic agent in combination with a second therapeutic agent comprising a non-genetic angiogenic, as claimed. As such, Branellec's disclosure AAVs a carrying a nucleic acid encoding GAX protein does not provide the claimed elements not taught in Isner to render the claimed invention upatentably obvious.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims 1, 18, 26 and 43 under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 3, 24, 25 and 27 under 35 U.S.C. § 103(a), as allegedly being unpatentably obvious over Isner (U.S. Patent No. 5,652,225) in view of Lennox et al., (US Patent No. 6,280,411, hereinafter "Lennox").

The Examiner concedes that Isner does not teach specifically a medical device wherein the polymer coating is about 1 to about 40 layers having a thickness of about 1 to about 40mm/layer of

coating or using the medical device to deliver a nucleic acid and a non-genetic agent to a cell. The Examiner opines that this shortcoming is overcome by Lennox which allegedly teaches medical devices coated with a polymer that is about 1 to 10mm in thickness with multiple layers. Applicants respectfully disagree.

As illustrated above, Isner does not teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent comprising a vector containing a first polynucleotide wherein the first polynucleotide encodes an angiogenic agent; in combination with a second therapeutic agent comprising a non-genetic therapeutic agent, wherein the non-genetic therapeutic agent is an angiogenic agent, wherein the second therapeutic agent does not include nitric oxide synthase, as claimed. Lennox also fails to teach a medical device comprising a biocompatible structure carrying a genetic material comprising a first therapeutic agent encoding an angiogenic agent in combination with a second therapeutic agent comprising a non-genetic angiogenic, as claimed. As such, Lennox's disclosure relating to polymer thickness and layer number does not supply the claimed elements not taught in Isner to render the claimed invention upatentably obvious.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Respectfully submitted,

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